REMARKS

Claims 1-5, 7-13, 27, 28, 30, 32-34, 51 and 52 are pending. New claims 77 and 78 are added herein. Claims 1-4, 7-9, 11, 27, 28, 30, 32-34, 51 and 52 are amended herein. The amendments add no new matter.

Rejections under 35 U.S.C. §112, Second Paragraph:

Claims 1 and 51 are rejected as indefinite. The Office Action states that "it is unclear how dissociation is detected." The Office Action continues:

> "It appears that in order to detect the dissociation of the binding partner polypeptides, the binding partner polypeptides would have to already be bound to something else and this binding detected. Then the detection of dissociation of the binding partner polypeptides would be performed."

Applicant has herein removed reference to the detection of dissociation from amended claims 1 and 51, which should be sufficient to obviate this ground of rejection.

Applicant has added herein new claims 77 and 78, which are specifically drawn to embodiments in which dissociation of the binding partner polypeptides, rather than association, is detected. Each of claims 77 and 78 includes the requirement in step "A" that the "one or more tagged binding partner polypeptides of (i) and said one or more binding partner polypeptides that correspond to said one or more tagged binding partner polypeptides associate." As such, the subsequent detection can detect dissociation. Applicant submits that new claims 77 and 78 are therefore definite.

The claims dependent from claims 1 and 51 have also been amended to add dependency from claims 77 and 78, respectively, in order to maintain coverage of the dissociation embodiments removed by amendment of the parent claims. The amendments add no new matter.

In view of the amendments, Applicant respectfully requests the withdrawal of the §112, second paragraph rejection of claims 1 and 51.

Claim 11 is rejected as indefinite "because it is unclear what relationship exists between the tagged binding partner, the detection molecule and the binding partner of step (ii) tagged."

The Office Action asks "Are there three labels present in the assay and if so are they the same or different?

Applicant submits that the specification states:

> "A tag allows for the interaction of a tagged binding partner polypeptide with a detection molecule or with another tag, such that the tag can be detected. Optionally, the tag can be directly detected." (page 56, lines 1-3)

The independent claims recite that the detector molecule comprises "a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules." That is, the tag on the tagged binding partner polypeptide of clause (i) of the independent claim (claim 1) permits the interaction of that polypeptide with the detector molecule such that the tag can be detected. Thus, the tag on the binding partner of clause (i) provides for indirect detection by association with the detector molecule. See also the specification at page 61, lines 9-11 which state "For indirect detection a tag is bound by a detection molecule which incorporates a detectable moiety (or a reporter region)."

Applicant submits that in the broadest sense of the claimed invention, e.g., those embodiments recited in claims 1, 51, 77 and 78, there is only required to be one tag or label, i.e., the tag on the tagged binding partner polypeptide recited in clause (i). This tag associates with the detector molecule to provide detection via the recited reporter molecule. The moieties that can be "tags" are described in the specification section titled "Tags" (page 55, line 15 to page 61, line 5). Although there is overlap between the moieties described in the specification that can be "tags" and those that can constitute the reporter molecule comprised by the detector molecule (described at page 62, lines 6-19) the separate terms "tag" and "reporter molecule" are retained for clarity. Thus, the limitation in dependent claim 11, that the one or more binding partner polypeptides of clause (ii) are tagged, introduces a second "tag." Where the tagged binding partner polypeptide of clause (i) is present with a binding partner of clause (ii) that is tagged according to claim 11, the method will involve two different tags and a detector molecule that comprises a reporter molecule.

In addressing the question raised in the Office Action, Applicant wishes to point out that while FRET detection, which requires one fluorescent label or quencher associated with each member of a binding pair, is a preferred embodiment, there are embodiments under which only one detectable moiety is associated with or becomes associated with the binding pair described in clauses (i) and (ii) of the broad claims. For example, the specification describes the use of fluorescence correlation spectroscopy, fluorescence anisotropy, and fluorescence polarization (see page 74, line 16 to page 77, line 2), each of which functions to determine binding partner interaction while only using one directly detectable label. Thus, while FRET, with its requirement for two fluorescent labels (or a label and a quencher), is preferred, there is ample support for methods that rely on a single label. Thus, while the broad claims require only a single tag plus a detector molecule that associates with that tag, the broad claims are complete as written and do not omit necessary elements.

In view of the above, Applicants submit that claim 11 as written is definite and respectfully request the withdrawal of the rejection under §112, second paragraph.

Rejection under 35 U.S.C. §103(a):

Claims 1, 3, 4, 7, 8, 27, 28, 30, 32-34 and 51 are rejected under 35 U.S.C. §103(a) as obvious over Blau et al. (WO 98/44350) in view of Colyer (WO 99/11774). The Office Action states that "Blau et al. disclose methods for detecting protein-protein interactions," that the methods taught "can be used to study other molecules which influence the interaction between the binding partners," that "the phosphorylation of one of the binding partners endows it to associate with another of the binding partners," that "the interactions can be detected by using reporter subunits (tag) which produce a chromogenic, fluorescent or luminescent signals," and that "the reporter subunits may comprise fluorophores, which are capable of detectable resonance energy transfer when they are closely associated." The Office Action states that "Blau et al. differ from the instant invention in failing to teach a detector molecule comprising a first region that associates with the tagged binding partner polypeptide and a second region comprising one or more reporter molecules," and that Blau et al. also fails to teach detecting binding or association of the binding partner polypeptides and the tagged binding partner polypeptides in both the presence and absence of candidate modulators."

The Office Action states that Colyer et al. discloses "a method for monitoring the activity of an enzyme comprising monitoring the addition or removal of a moiety," mixing a labeled (tag) polypeptide comprising a coiled-coil with its binding partner," and mixing with the labeled polypeptide a second coiled-coil comprising a label (detection molecule)." The Office Action also states that Colyer et al. teach "methods for screening a candidate modulator." The Office Action concludes that it would have been obvious to one of ordinary skill in the art to "incorporate detection molecules, tag molecules and candidate modulators as taught by Colyer et al. into the method of Blau et al. because Colyer et al. shows that the use of these coiled-coil tag and detection molecules provides for efficient means of monitoring and/or modulating post-translational protein modification." Applicant respectfully disagrees.

Applicant submits that Colyer et al. does not teach the use of a tagged binding partner polypeptide, a binding partner polypeptide that corresponds to the tagged binding partner polypeptide, *and* a detector molecule comprising a first region that associates with a tagged binding partner polypeptide and a second region comprising one or more reporter molecules, as required by the claims. That is, Colyer et al. does not teach the use of two binding partners *and* a detector molecule, as is required by claims 1 and 51. Colyer et al. states:

> "In particular, this invention contemplates assays in which the amount- or activity of a modifying enzyme in a sample is determined by contacting the sample with *a pair of polypeptides* comprising coiled-coil motifs differentially labeled with fluorescent proteins, as described above, and measuring changes in fluorescence of the donor moiety, the acceptor moiety or the relative fluorescence of both." (Colyer et al., page 38, lines 1-5; emphasis added)

Thus, while Colyer et al. may teach the use of a pair of differentially fluorescently-labeled polypeptides having coiled coil motifs, nowhere in Colyer et al. is it taught to *also* add a detector molecule comprising a first region that associates with one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules, in addition to such a pair of polypeptides.

As noted above, the Office Action acknowledges that Blau et al. fails "to teach a detector molecule comprising a first region that associates with the tagged binding partner polypeptide and a second region comprising one or more reporter molecules." Because Colyer et al. also fails to teach the use of an added detector molecule in addition to one or more tagged binding

partner polypeptides and one or more binding partner polypeptides that correspond to the one or more tagged binding partner polypeptides, as required by each of claims 1 and 51, Applicant submits that the Colyer et al. reference cannot render obvious the invention of claims 1, 51 or claims dependent from them. Applicant respectfully requests withdrawal of the §103(a) rejection of claims 1, 3, 4, 7, 8, 27, 28, 30, 32-34 and 51 over this combination of references.

Claims 2, 5, 9-13 and 52 are rejected under 35 U.S.C. §103(a) as obvious over Blau et al. in view of Colyer et al. as applied above, in further view of references including Heroux et al., Levin et al., and Wild et al. As discussed above, neither Blau et al. nor Colyer et al. teaches one or more detector molecules comprising a first region that associates with said one or more tagged binding partner polypeptides and a second region comprising one or more reporter molecules as required by each of these claims. Applicant submits that none of the Heroux et al., Levin et al. or Wild et al. references supplies this limitation. As such, Applicant submits that the invention of claims 2, 5, 9-13 and 52 cannot be obvious over any combination of these references. Applicant respectfully requests the withdrawal of this §103(a) rejection of claims 2, 5, 9-13 and 52 over this combination of references.

In view of the above, Applicant submits that all issues raised in the Office Action have been addressed. Applicant respectfully requests reconsideration f the claims.

Respectfully submitted,

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